

**PCT**WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau

## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>6</sup> : <b>A61K 31/70, C07H 1/00, 17/08</b>		<b>A1</b>	(11) International Publication Number: <b>WO 00/32203</b>
			(43) International Publication Date: <b>8 June 2000 (08.06.00)</b>
(21) International Application Number: <b>PCT/US99/28368</b>			(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
(22) International Filing Date: <b>30 November 1999 (30.11.99)</b>			
(30) Priority Data: <b>60/110,298 30 November 1998 (30.11.98) US</b>			
(71) Applicant (for all designated States except BB US): <b>TEVA PHARMACEUTICAL INDUSTRIES LTD. [IL/IL]; 5 Basel Street, P.O. Box 3190, 49131 Petah Tiqva (IL).</b>			
(71) Applicant (for BB only): <b>TEVA PHARMACEUTICALS USA, INC. [US/US]; 1515 Delp Drive, Kulpsville, PA 19443 (US).</b>			
(72) Inventors; and (75) Inventors/Applicants (for US only): <b>SINGER, Claude [IL/IL]; 8 David Elazar Street, Kfar Sava (IL). ARONHEIM, Judith [IL/IL]; 8 Hava Lutzky Street, Rehovot (IL).</b>			
(74) Agents: <b>BRAINARD, Charles, R. et al.; Kenyon &amp; Kenyon, One Broadway, New York, NY 10004 (US).</b>			Published With international search report.
(54) Title: <b>ETHANOLATE OF AZITHROMYCIN, PROCESS FOR MANUFACTURE, AND PHARMACEUTICAL COMPOSITIONS THEREOF</b>			
(57) Abstract  A novel, non-hygroscopic form of azithromycin is disclosed, as well as a method for preparing it by the gradual crystallization of azithromycin from ethanol by the addition of a minimal amount of water to effect crystal formation. Pharmaceutical compositions containing this novel form of azithromycin are also disclosed.			

BEST AVAILABLE COPY

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

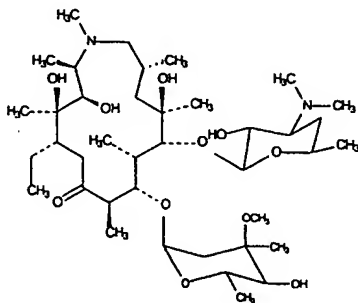
**ETHANOLATE OF AZITHROMYCIN, PROCESS FOR  
MANUFACTURE, AND PHARMACEUTICAL COMPOSITIONS  
THEREOF**

## **FIELD OF THE INVENTION**

This invention relates to a new ethanolate of azithromycin, processes for its manufacture, and pharmaceutical compositions containing the new ethanolate.

## **BACKGROUND OF THE INVENTION**

Azithromycin, 9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin A,  
having the formula



is a semi-synthetic macrolide antibiotic related to erythromycin A, useful for treating infections caused by susceptible microorganisms. This invention provides a new non-hygroscopic form of azithromycin, processes for its manufacture, and pharmaceutical compositions containing it.

Azithromycin may be made by methods described in U.S. Patent Nos. 4,517,359 and 4,474,768. According to European Patent Application EP 298,650, the azithromycin obtained by these methods is a hygroscopic monohydrate. Because of its

hygroscopic nature, this monohydrate is difficult to prepare and maintain in a form having a constant, reproducible water-content, and is particularly difficult to handle during formulation. EP 298,650 describes a dehydrate form of azithromycin that is less hygroscopic than the previously known monohydrate. The method described in EP  
5 298,650 for making the dehydrate form is by crystallization from tetrahydrofuran, hexane and water.

Chinese Patent Application CN 1,093,370, describes an azithromycin crystal having water content of 4–6%. This form of azithromycin is stated as being less hygroscopic than the dehydrate described in EP 298,650. The method disclosed in CN  
10 1,093,370 for making the described form of azithromycin is by crystallization from acetone and water.

### **SUMMARY OF INVENTION**

The present invention provides a new ethanolate of azithromycin that is less hygroscopic than azithromycin monohydrate. The new ethanolate has an ethanol content  
15 of about 1.5% to about 3% and a water content of about 2% to about 4%.

The present invention also provides a method of making an ethanolate of azithromycin, comprising the steps of:

dissolving azithromycin in ethanol,  
adding water to the azithromycin solution such that crystallization of the  
20 azithromycin begins and a suspension is formed, and  
isolating the crystals of azithromycin.

The present invention further provides a pharmaceutical composition

comprising a therapeutic amount of an ethanolate of azithromycin in accordance with the present invention and a pharmaceutically acceptable carrier.

### **BRIEF DESCRIPTION OF THE DRAWINGS**

5           Figure 1 is a comparison of hygroscopicity of the azithromycin ethanolate of the present invention and azithromycin monohydrate over a range of relative humidity, based upon data provided in EP 298,650.

          Figure 2 is a characteristic powder X-ray diffraction pattern of the azithromycin ethanolate of the present invention.

10

### **DETAILED DESCRIPTION OF THE INVENTION**

          The present invention discloses a new ethanolate of azithromycin that is less hygroscopic than the prior art monohydrate, and has an ethanol content of about 1.5 to about 3% and water content of about 2 to about 4%. Preferably the ethanol content is  
15       between about 1.5% and about 2.5%. Preferably the water content is between about 2.5% and about 3.5%. A comparison of the hygroscopicity of the ethanolate of the present invention and azithromycin monohydrate can be found at Figure 1.

          The process for manufacture of azithromycin ethanolate of the present invention utilizes the fact that water is a poorer solvent for azithromycin than ethanol, so  
20       that the addition of water to a solution of azithromycin in ethanol causes crystallization. Second, heating a solution of azithromycin in ethanol in the presence of water promotes crystallization.

In accordance with the process aspects of the invention, azithromycin is dissolved in absolute ethanol, in a ratio of about 2.5:1 (ethanol:azithromycin by weight) at a temperature of between about 10°C and about 80°C, preferably at about 20° to about 30°C. A minimal amount of water is added, i.e. an amount no greater than 20% (by weight  
5 versus ethanol), preferably about 6 to about 16%. The solution is heated slowly at a constant temperature gradient over a first time interval of about 2 to about 18 hours, preferably about 3 to about 8 hours, reaching a maximum temperature of about 30 to about 80°C and preferably about 40 to about 60°C at the end of the first time interval. Crystallization appears to begin in the temperature range of about 30–45°C. During the  
10 first time interval, the water content of the solution is gradually increased, but to a concentration of no more than about 50%.

At the end of the first time interval, the resulting suspension is maintained at the maximum temperature for a second time interval of about 1 to about 18 hours, preferably about 1 to about 4 hours. During the second time interval, additional water is  
15 added to complete the crystallization process.

At the end of the second time interval, the suspension is cooled using a constant temperature gradient over a third time interval of about 1 to about 18 hours, preferably about 2 to about 4 hours, reaching a final temperature of about 20°C. The resulting precipitate is collected by filtration and dried to constant weight. Table 1 shows  
20 the water content of the new azithromycin ethanolate using Karl Fisher analysis and ethanol content using gas chromatography.

**Table 1. Ethanol and Water Content of Azithromycin Ethanolate**

Batch	Ethanol Content (gas chromatography)	Water Content (Karl-Fischer)
	% w/w (weight/weight)	% w/w
A	2.2	3.24
B	2.3	2.46
C	2.2	2.71
D	2.3	2.77
E	2.2	3.28
F	1.52	2.70
G	1.7	3.40

In accordance with the present invention, the new ethanolate of azithromycin may be prepared as pharmaceutical compositions that are particularly useful for the treatment of infections caused by susceptible microorganisms. Such compositions comprise the new ethanolate of azithromycin with pharmaceutically acceptable carriers and/or excipients.

For example, these compositions may be prepared as medicines to be administered orally, parenterally, rectally, transdermally, buccally, or nasally. Suitable forms for oral administration include tablets, compressed or coated pills, dragees, sachets of powder for reconstitution, hard or gelatin capsules, sub-lingual tablets, syrups and suspensions. Suitable forms for parenteral administration include an aqueous or non-aqueous solution or emulsion, while for rectal administration suitable forms include

suppositories with hydrophilic or hydrophobic vehicles. For topical application the invention provides ointments or aerosol formulations known in the art; for transdermal delivery there are provided suitable delivery systems as known in the art. For nasal delivery there are provided suitable aerosol delivery systems known in the art.

5     **Experimental Details**

Hygroscopicity profiles were obtained by maintaining samples in controlled humidity chambers for a period of two weeks, followed by Karl Fisher analysis of water content.

Gas chromatograms were obtained using a Hewlett-Packard 5890 gas  
10     chromatograph.

Powder x-ray diffraction patterns were obtained by methods known in the art using a Philips X-Ray powder diffractometer, Goniometer model 1050/70 at a scanning speed of 2° per minute, with a Cu radiation of  $\lambda = 1.5418 \text{ \AA}$ .

This invention will be better understood from the Example that follows.

15     However, the examples illustrate, but do not limit, the invention. Those skilled in the art will readily appreciate that the specific methods and results discussed are merely illustrative of the invention as described more fully in the claims that follow thereafter.

**EXAMPLE**

20     **Preparation of Azithromycin Ethanolate.**

Ten g of azithromycin crude was introduced into a 0.25 liter three-necked flat flanged jacketed vessel equipped with a mechanical stirrer, a condenser and thermometer



and containing 30 ml of absolute ethanol at 20°C. Three ml of water at 20°C were added and the solution was heated at a constant temperature gradient so as to reach 55°C after 4 hours. Between 35°C and 55°C, additional water having a total volume of 11 ml was slowly added at regular time intervals. When 55°C was reached, the resulting suspension  
5 was maintained at this temperature for 2 hours, during which an additional 49 mL of water was added. The suspension was then cooled from 55°C to 20°C over 2 hours. The precipitate was filtered. After drying, 9 g of azithromycin ethanolate were obtained.

Although certain presently preferred embodiments of the invention have been  
10 described herein, it will be apparent to those skilled in the art to which the invention pertains that variations and modifications of the described embodiments may be made without departing from the spirit and scope of the invention. Accordingly, it is intended that the invention be limited only to the extent required by the appended claims and the applicable rules of law.

15

## WE CLAIM

1. An ethanolate of azithromycin having an ethanol content of about 1.5% to about 3%.

5

2. The ethanolate of claim 1, having a water content of about 2% to about 4%.

3. The ethanolate of claim 2, wherein the water content is between about 2.5% and about 3.5%

10

4. The ethanolate of claim 1, wherein the ethanol content is about 1.5% to about 2.5%.

5. The ethanolate of claim 4, wherein the water content is about 2% to about 4%.

15

6. The ethanolate of claim 5, wherein the water content is between about 1.5% and about 2.5%.

7. An ethanolate of azithromycin that is characterized by a powder x-ray diffraction pattern substantially as depicted in Figure 2.

20

8. A method of making an ethanolate of azithromycin 1, comprising the steps of:  
dissolving azithromycin in ethanol,

adding water to the azithromycin solution such that crystallization of the azithromycin begins and a suspension is formed, and  
isolating the crystals of azithromycin.

5           9.     The method of claim 9, further comprising the step of maintaining the suspension at a temperature from about 30° to about 80°C for a period of time.

10           10.    The method of claim 9 wherein additional water is added to the suspension, and the suspension is held at a temperature from about 30° to about 80°C for about 1 to about 18 hours.

11.     The method of claim 10, wherein the suspension is cooled to about 20°C prior to isolating the crystals of azithromycin.

15           12.    The method of claim 8, wherein the ethanolate has an ethanol content of about 1.5% to about 3%.

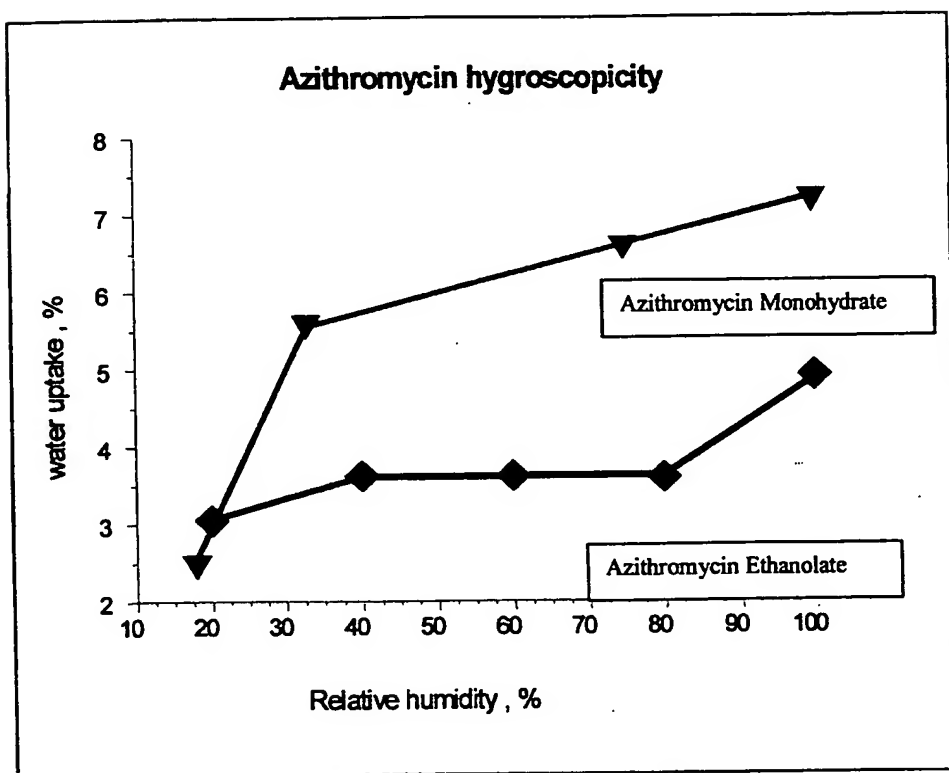
13.     The method of claim 12, wherein the ethanolate has a water content of about 2% to about 4%.

20           14.    The method of claim 8, wherein the ethanolate is characterized by a powder x-ray diffraction pattern substantially as depicted in Figure 2.

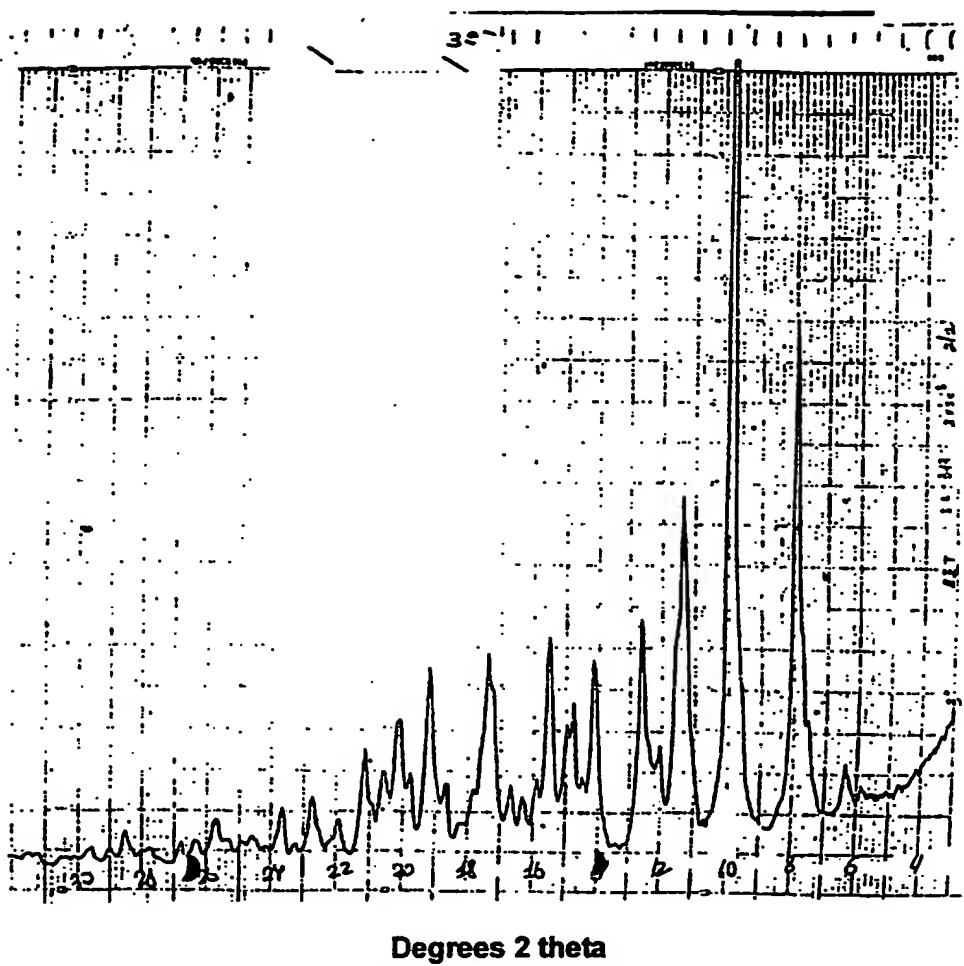
15. A pharmaceutical composition comprising a therapeutically effective amount of the ethanolate of the claim 1 and a pharmaceutically acceptable carrier.

**FIGURE 1**

Comparison of hygroscopicity between the new ethanolate of azithromycin and hygroscopic azithromycin monohydrate (based upon data provided in EP 298,650, pg. 4, lines 41-44).



2/2

**FIGURE 2**

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US99/28368

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 31/70; C07H1/00, 17/08

US CL :514/29; 536/7.2, 7.4, 18.5

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/29; 536/7.2, 7.4, 18.5

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 89/00576 A1 (PFIZER INC.) 26 January 1989, (26-01-1989) page 2, lines 5-12.	1-15



Further documents are listed in the continuation of Box C.



See patent family annex.

•

Special categories of cited documents:

\*A\*

document defining the general state of the art which is not considered to be of particular relevance

\*B\*

earlier document published on or after the international filing date

\*L\*

document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

\*O\*

document referring to an oral disclosure, use, exhibition or other means

\*P\*

document published prior to the international filing date but later than the priority date claimed

\*T\*

later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\*X\*

document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\*Y\*

document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

\*A\*

document member of the same patent family

Date of the actual completion of the international search

15 FEBRUARY 2000

Date of mailing of the international search report

17 MAR 2000

Name and mailing address of the ISA/US  
Commissioner of Patents and Trademarks  
Box PCT  
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

ELLI PESELEV

Telephone No. (703) 308-1235

**This Page is Inserted by IFW Indexing and Scanning  
Operations and is not part of the Official Record**

## **BEST AVAILABLE IMAGES**

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☒ BLACK BORDERS
- ☐ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES
- ☐ FADED TEXT OR DRAWING
- ☐ BLURRED OR ILLEGIBLE TEXT OR DRAWING
- ☐ SKEWED/SLANTED IMAGES
- ☐ COLOR OR BLACK AND WHITE PHOTOGRAPHS
- ☐ GRAY SCALE DOCUMENTS
- ☐ LINES OR MARKS ON ORIGINAL DOCUMENT
- ☐ REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY
- ☐ OTHER: \_\_\_\_\_

**IMAGES ARE BEST AVAILABLE COPY.**

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.